This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199856679 B2
(10) Patent No. 726147

(54) Title
Novel erythromycin derivatives, method of preparation and application as medicines

(51)[6] International Patent Classification(s)
C07H 017/08 A61K 031/70

(21) Application No: 199856679 (22) Application Date: 1997.12.22

(87) WIPO No: W098/28316

(30) Priority Data

(31) Number	(32) Date	(33) Country
96/15830	1996.12.23	FR

(43) Publication Date : 1998.07.17
(43) Publication Journal Date : 1998.09.10
(44) Accepted Journal Date : 2000.11.02

(71) Applicant(s)
Hoechst Marion Roussel

(72) Inventor(s)
Constantin Agouridas; Jean-Francois Chantot

(74) Agent/Attorney
CALLINAN LAWRIE,Private Bag 7,KEW VIC 3101

OPI DATE 17/07/98 APPLN. ID 56679/98
AOJP DATE 10/09/98 PCT NUMBER PCT/FR97/02380

AU9856679

DEN

3 (PCT)

(51) Classification internationale des brevets 6 : C07H 17/08, A61K 31/70 — A1

(11) Numéro de publication internationale: WO 98/28316

(43) Date de publication internationale: 2 juillet 1998 (02.07.98)

(21) Numéro de la demande internationale: PCT/FR97/02380

(22) Date de dépôt international: 22 décembre 1997 (22.12.97)

(30) Données relatives à la priorité:
96/15830 23 décembre 1996 (23.12.96) FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: HOECHST MARION ROUSSEL [FR/FR]; 1, Terrasse Bellini, F-92800 Puteaux (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants *(US seulement)*: AGOURIDAS, Constantin [FR/FR]; 107, boulevard de Strasbourg, F-94130 Nogent sur Marne (FR). CHANTOT, Jean-François [FR/FR]; 7, rue Pasteur, F-94130 Nogent sur Marne (FR).

(74) Mandataire: TONNELLIER, Marie-José; Hoechst Marion Roussel, 102, route de Noisy, F-93235 Romainville Cedex (FR).

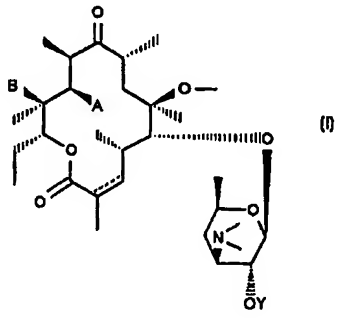
(81) Etats désignés: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, brevet ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Publiée

Avec rapport de recherche internationale.

(54) Title: NOVEL ERYTHROMYCIN DERIVATIVES, METHOD OF PREPARATION AND APPLICATION AS MEDICINES

(54) Titre: NOUVEAUX DERIVES DE L'ERYTHROMYCINE, LEUR PROCEDE DE PREPARATION ET LEUR APPLICATION COMME MEDICAMENTS



(I)

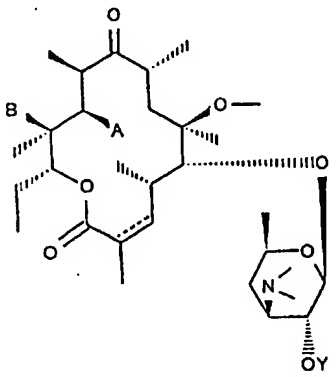
(57) Abstract

The invention concerns compounds of formula (I) in which X represents a CH_2 or NH group, R represents a $(CH_2)_nAr$, $N=(CH_2)_nAr$ or $N=CH(CH_2)_nAr$ radical, in which n represents a whole number ranging between 1 and 6 an Ar represents an aryl or heteroaryl, optionally substituted, the dotted lines representing an optional double bond in 2(3), and Y represents a hydrogen atom or an organic carboxylic acid radical containing up to 18 carbon atoms and their additive salts with acids. The compounds of formula (I) have antibiotic properties which enable their use as medicines.

New derivatives of erythromycin, a method for preparing them, and their use as medicines

The present invention concerns new derivatives of erythromycin, their preparation method, and their use as medicaments.

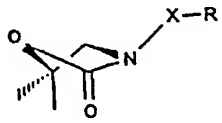
The objects of the invention are compounds with formula (I):



(I)

in which:

- either A and B represent an OH radical,
- or B represents an OH radical and A forms a double bond with the carbon atom on which it is located and with the carbon atom at 10,
- or A and B together form a carbonate radical,
- or A and B together with the carbon atoms on which they are located form a cycle:



in which X represents a CH_2, NH or SO_2 group, R represents a $(CH_2)_n Ar$, $N\text{-}(CH_2)_n Ar$ or $N{=}CH(CH_2)_n Ar$ radical in which n is an integer between 1 and 6 and Ar represents a possibly substituted aryl or heteroaryl radical,

AUSTRALIAN PATENT OFFICE

the broken lines represent a possible double bond at 2(3), and Y represents a hydrogen atom or the residue of a carboxylic organic acid containing up to 18 carbon atoms and their addition salts with acids.

The aryl radical may be a phenyl or naphthyl radical.

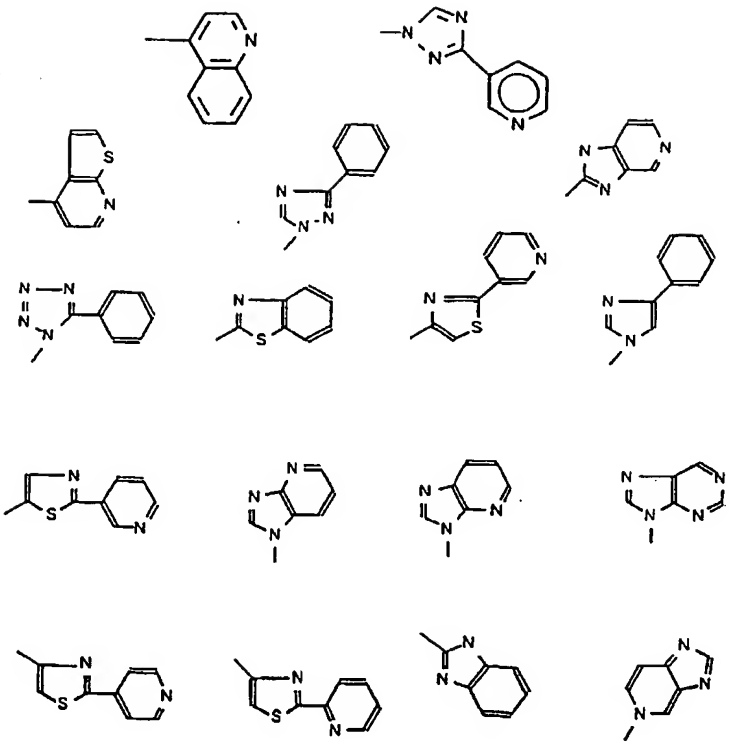
The aryl radical may also be a substituted or unsubstituted heterocyclic radical such as any of the following radicals: thienyl, furyl, pyrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl or isopyrazolyl, a pyridyl, pyrimidyl, pyridazinyl or pyrazinyl radical, or even an indolyl, benzofurannyl, benzothiazyl or quinoleinyl radical.

These aryl radicals may comprise one or more groups chosen from among the following radicals: hydroxyl, halogen atoms, the NO_2, NH_2 and C≡N radicals, and the alkyl, alkenyl or alkynyl, O-alkyl, O-alkenyl or O-alkynyl, S-alkyl, S-alkenyl or S-alkynyl and N-alkyl, N-alkenyl or N-alkynyl radicals, containing up to 12 carbon atoms possibly substituted by one or more halogen atoms, the radical

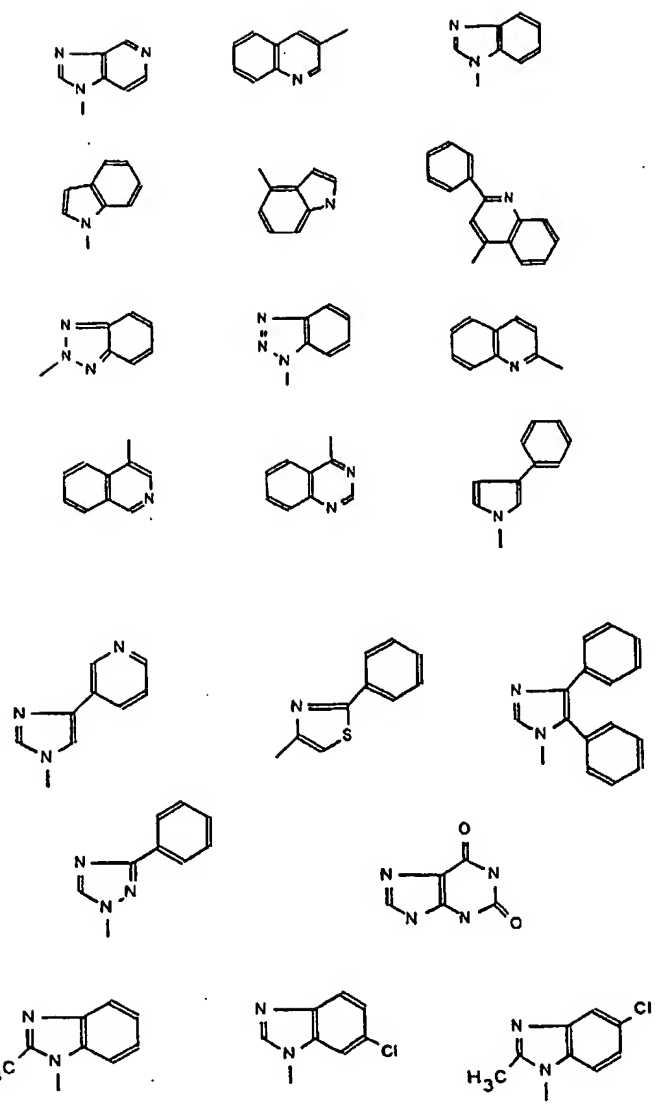
, in which Ra and Rb may be the same or different and represent a hydrogen atom or an alkyl radical containing up to 12 carbon atoms, the radical

, in which R_3 represents an alkyl radical containing up to 12 carbon atoms, or a possibly substituted aryl or heteroaryl radical, the aryl, O-aryl or S-aryl carboxylic or aryl, O-aryl or S-aryl heterocyclic radicals with 5 or 6 links comprising one or more hetero-atoms, possibly substituted by one or more of the substituents mentioned above.
As a preferred heterocycle, the following may be mentioned among others:

AUSTRALIAN PATENT OFFICE



AUSTRALIAN PATENT OFFICE



and the heterocyclic radicals envisaged in European Patent Applications 487411, 596802, 676409 and 680967. These preferred heterocyclic radicals may be substituted

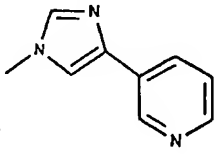
AUSTRALIAN PATENT OFFICE

by one or more functional groups.

Among the addition salts with acids, the salts formed with the following acids may be mentioned: acetic, proprionic, trifluoroacetic, malic, tartaric, methanesulphonic, benzenesulphonic, p-toluenesulphonic, and in particular stearic, ethylsuccinic or laurylsulphonic acids.

Particular objects of the invention are compounds with formula (I), which correspond to formula (I) in which X represents a CH_2 or NH group, R represents a $(CH_2)_n$ Ar, N-$(CH_2)_n$ Ar or N=CH$(CH_2)_n$ Ar radical in which n is an integer between 1 and 6 and AR represents an aryl or heteroaryl radical, possibly substituted, the broken lines represent a possible double bond at 2(3), and Y represents a hydrogen atom or the residue of a carboxylic organic acid containing up to 18 carbon atoms, and their addition salts with acids.

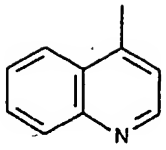
More particularly still, the objects of the invention are compounds with formula (I), in which the broken lines represent a double bond at 2(3), those in which Y represents a hydrogen atom and those in which R represents a $(CH_2)_n$ Ar group, where n and Ar mean the same as before. Among the preferred compounds of the invention may be mentioned in particular the compounds with formula (I) in which R represents a $(CH_2)_3$ Ar, $(CH_2)_4$ Ar or $(CH_2)_5$ Ar radical, and especially the compounds in which Ar represents a possibly substituted:



radical

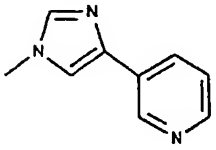
or a possibly substituted:

AUSTRALIAN PATENT OFFICE



radical

as for example the compounds with formula (I) in which Ar represents a:



radical.

More particularly, the object of the invention is the compound of Example 1.

Products with the general formula (I) show very good antibiotic action against gram-positive bacteria such as staphylococci, streptococci and pneumococci.

Thus, the compounds of the invention can be used as medicaments for the treatment of infections by sensitive microbes and especially in the treatment of staphylococcoses, such as staphylococcal septicaemias, malignant staphylococcoses of the face or skin, pyodermites, septic or suppurating wounds, furuncles, anthrax, phlegmons, erysipelis and acne, staphylococcoses inducing acute primitive or post-influenza chest pains, bronchial pneumonia, pulmonary suppuration, streptococcoses inducing acute chest pains, otitis, sinusitis, scarlatina, and pneumococcoses such as pneumonia or bronchitis; brucellosis, diphtheria and gonococcosis.

The products of the present invention are also active against infections due to microbes such as Haemophilus influenzae, Rickettsieae, Micoplasma pneumoniae, Chlamydia, Legionella, Ureaplasma, Toxoplasma, or to microbes of the Mycobacterium type.

Thus, further objectives of the present invention are medicaments and in particular antibiotic medicaments,

AUSTRALIAN PATENT OFFICE

based on the products with formula (I) as defined above and their addition salts with pharmaceutically acceptable mineral or organic acids.

More particular objectives of the present invention are medicaments, especially antibiotic medicaments, based on the products of Example 1 and their pharmaceutically acceptable salts.

Further objects of the invention are pharmaceutical compositions containing at least one of the medicaments defined above as the active ingredient.

These compositions can be administered via the oral, rectal or parenteral routes, or locally by topical application to the skin and the mucosa, but the preferred route of administration is the oral route.

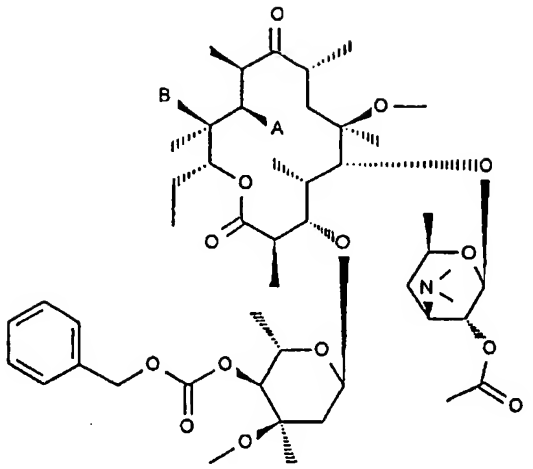
They may be solids or liquids, and are presented in the pharmaceutical forms in common use for medication in man, for example simple tablets or dragées, gelatine capsules, granulates, suppositories, injectable preparations, ointments, creams or gels; they are prepared by the usual methods. The active ingredient(s) are incorporated together with the excipients ordinarily used in such pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting agents, dispersants or emulsifiers, and preservatives.

The compositions can also take the form of a powder intended to be freshly dissolved in a suitable vehicle, for example sterile, apyrogenic water.

The dose administered varies depending on the affection treated, the subject involved, the route of administration and the product considered. For example, it may range from 50 mg to 300 mg per day via the oral route in adults, in the case of the product of Example 1.
A further object of the invention is a process characterised

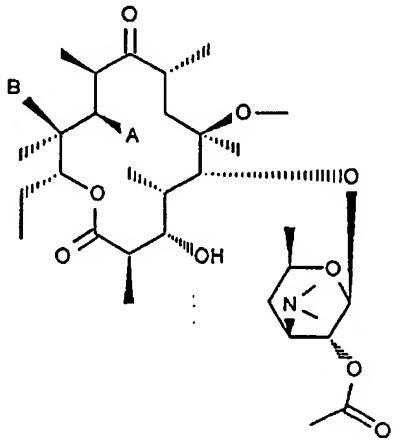
AUSTRALIAN PATENT OFFICE

in that a compound with formula II:



(II)

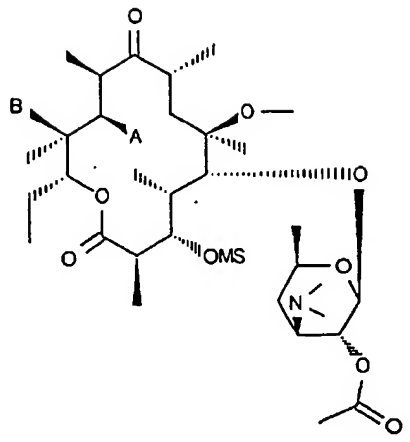
in which A and B mean the same as before, is subjected to the action of an agent which splits the glycoside bond to free the hydroxyl at 3 and obtain a compound with formula (III):



(III)

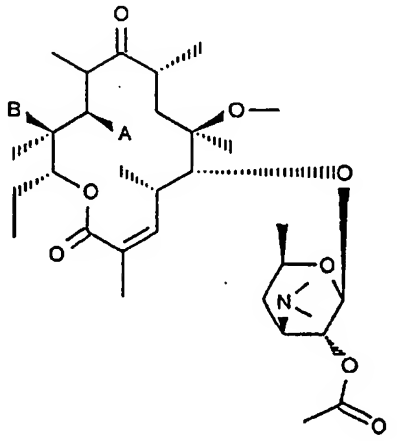
and blocks the hydroxyl at 3 in the form of a mesylate to obtain the compound with formula (IV):

AUSTRALIAN PATENT OFFICE



(IV)

which is subjected to the action of a base to obtain the compound with formula (V):

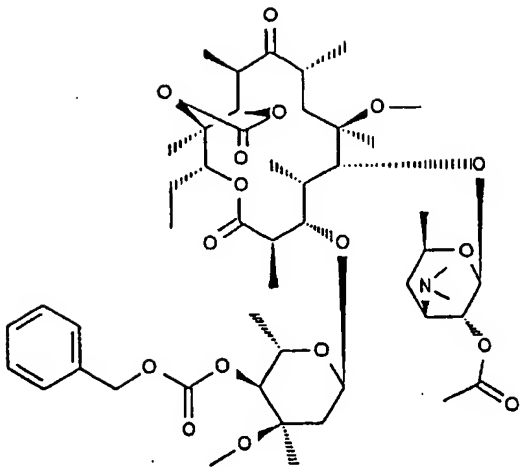


(V)

which, if desired, is subjected to the action of an agent which splits the hydroxyl at 2' to obtain the corresponding compound with formula (I).

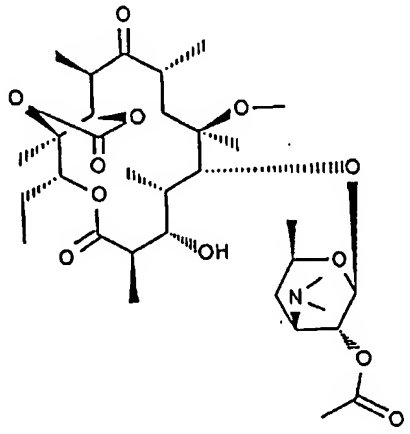
More particularly, an object of the invention is a process for preparing compounds with formula (I), characterized in that a compound with formula (II_A):

AUSTRALIAN PATENT OFFICE



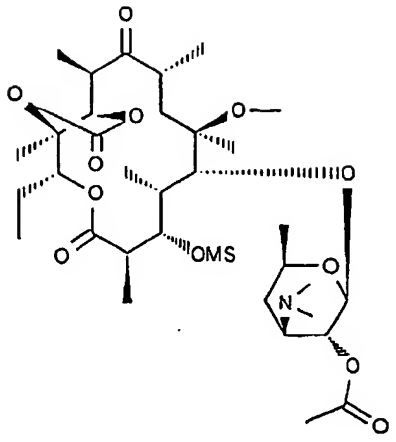
(II_A)

is subjected to the action of an agent which splits the glycoside bond to free the hydroxyl at 3 and obtain a compound with formula (III_A):



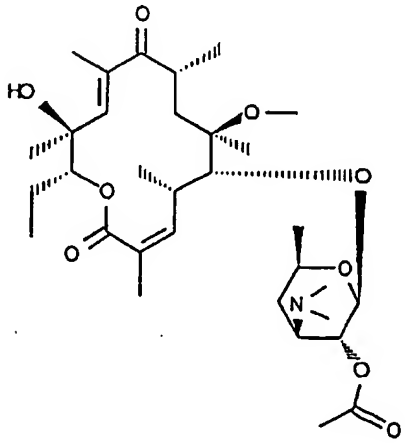
(III_A)

and blocks the hydroxyl at 3 in the form of a mesylate to obtain the compound with formula (IV_A):



(IV_A)

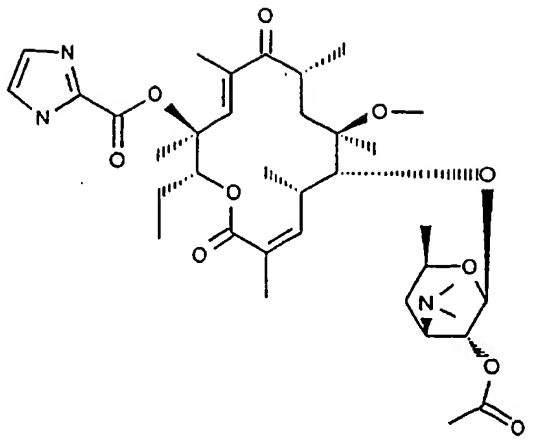
which is subjected to the action of a base to obtain the compound with formula (V_A):



(V_A)

which is subjected to the action of carbonydiimidazole to obtain the compound with formula (VI):

AUSTRALIAN PATENT OFFICE

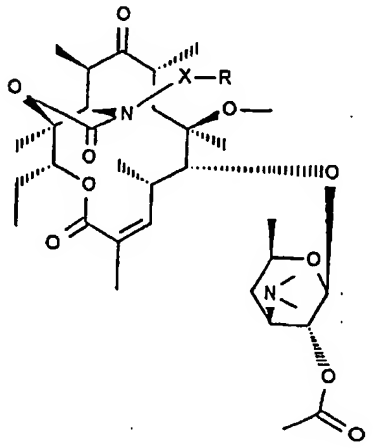


(VI)

which is subjected to the action of the compound with formula (VII):

$$RXNH_2 \qquad (VII)$$

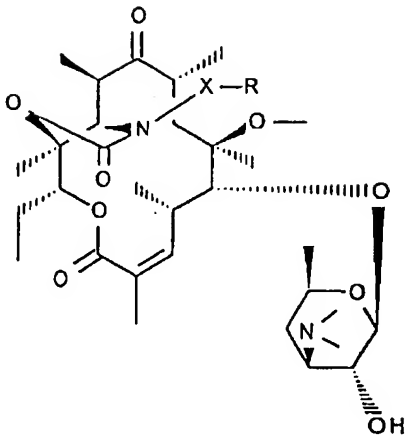
in which R and X have the same meaning as before, to obtain the compound with formula (I_A):



(I_A)

and, if desired, to free the hydroxyl at 2′ to obtain the compound with formula (I_B):

AUSTRALIAN PATENT OFFICE



(I_B)

which, if desired, is subjected to the action of an agent which esterifies the hydroxyl at 2', and/or to the action of an agent which reduces the double bond at 2(3) and/or to the action of an acid in order to form the salt thereof.

The products with formula (I) used as starting products are known products which can be prepared in accordance with the method described by BAKER et al. In J. Org. Chem. 1988, 53, 2340, 2345.

In a preferred embodiment:

- the cladinose at position 3 is hydrolysed using concentrated hydrochloric acid,
- mesylation is carried out using methanesulphonic acid or one of its derivatives, for example methanesulphonic anhydride,
- the base used to transform the compound with formula (IV) into the compound with formula (V) is a diazabicycloundecene, for example DBU (or 1,8-diazabicyclo[5-4-0]undec-7-ene), or diazabicyclononene, or 2,6-lutidine, or 2,4,6-collidine, or tetramethylguanidine,
- the transition from the compound with formula (V) to the compound with formula (VI) is effected using carbonyldiimidazole,
- the reaction of the compound with formula (IV) with the compound having

AUSTRALIAN PATENT OFFICE

formula (VII) $RXNH_2$ takes place in the presence of a base, for example a diazabicycloundecene such as DBU, or diazabicyclononene, or 2,6-butidine, or 2,4,6-collidine, or tetramethylguanidine.

The compounds obtained when carrying out the process are new products and are themselves objects of the present invention.

Thus, further objects of the invention are new chemical products, namely the compounds with formulae (III), (IV), (V) and (VI).

More particularly, objects of the invention are new chemical products, namely the products whose preparation is described below in the experimental section.

EXAMPLE 1: 2,3-didehydro-11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexapyranosyl)oxy]-6-O-methyl-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-erythromycin

STAGE A: 11,12-carbonate cyclic 2'-acetate of 3-O-de(2,6-ideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-6-O-methyl-erythromycin.

A mixture of 17.9 g of 11,12-carbonate cyclic 2'-acetate 4"-(phenylmethyl carbonate) of 6-O-methyl-erythromycin and 360 ml of methanol is cooled to 5°C. 90 ml of a concentrated hydrochloric acid solution are added. The temperature is allowed to rise to ambient temperature and the solution is stirred for 6 h. The reaction medium is poured over an ice-ammonia mixture, extracted with ethyl acetate, washed with water, dried, and concentrated under reduced pressure. 11.62 g of a product crystallised in diethyl ether are isolated. The crystals obtained are dried by decanting, washed, and dried under vacuum at 70°C. 7.83 g of the expected product are obtained. F = 226 ~ 228°C.

NMR - $CDCl_3$ ppm

0.87 (t) : $\underline{CH_3}$-CO_2; 0.95 (d) : 4-Me; 1.11 (d) : 8-Me; 1.19 (d) : 10-Me; 1.23 (d) : 2-Me; 1.27 (d) : 5'-Me; 1.28-1.49 : 6 and 12-Me; ~ 1.34 and 1.73 : CH_2 at 4'; ~ 1.49 and 1.63 : CH_2 at 7; ~ 1.59 and 1.90 : CH_2 at 14; 1.86 (d) : 3-OH; 1.98n(dq) : H_4; 2.07 (s) : OAc; 2.26 (s) : $N(Me)_2$;

2.58 (m) : H_8; 2.71 (m) : H_2 and H_3'; 2.92 (s) : 6-OMe; 2.95 (q) : H_{10}; 3.48 (m) : H_3 and H_5'; 3.70 (d) : H_5; 4.58 (d) : H_1'; 4.74 (s) : H_{11}; 4.75 (dd) : H_2; 5.13 (dd) : H_{13}.

STAGE B: 11,12-carbonate cyclic 2'-acetate 3-(methanesulphonate) of 3-O-de(2,6-ideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-6-O-methyl-erythromycin.

A mixture containing 9.20 g of the product obtained in Stage A, 60 ml of methylene chloride and 7.90g of DMAP is cooled to 10°C. 5.99 g of methanesulphonic anhydride are added. The reaction mixture is stirred at ambient temperature for 17 h 30 min. The reaction mixture is poured over ice, extracted with methylene chloride, washed with water and then with saline water, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. 11.078 g of the product expected are isolated. F = 194 ~ 196°C.
NMR $CDCl_3$ ppm
0.89 (t) : CH^{3-CH_2}; 1.00 (d) : 4-Me; 1.12 (d) : 8-Me; 1.19 (d) : 10-Me; 1.21 (d) : 5-Me; 1.27 (d) : 2-Me; 1.48-1.34 : 6 and 12-Me; ~ 1.48 and 1.57 : CH_2 at 7; ~ 1.25 and 1.70 : CH_2 at 4'; ~1.62 and ~1.91 : CH_2 at 14; 2.02 (dq) : H_4; 2.06 (3) : OAc; 2.25 (s) : $N(Me)_2$; 2.63 (m) : H_8; 2.72 (m) : H_3'; 2.93 (ql) : H_{10}; 2.99 : 6-OMe; 2.99 (masked) : H_2; 3.13 (s) : OSO_2Me; 3.57 (m): H_5'; 4.01 (d, J = 5) : H_5; 4.50 (d) : H_1'; 4.68 (sl) : H_{11}; ~4.71 (dd) : H_2'; 4.74 (d) : H_3; 5.10 (dd) : H_{13}.

STAGE C: 2'-acetate of 11-deoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-2,3,10,11-tetradehydro-erythromycin.

A mixture of 9.56 g of the product obtained in Stage B, 95 ml of acetone and 15.5 ml of DBU is refluxed for 6 h 30 min. The reaction mixture is poured over an ice/water mixture. The precipitate is filtered, dissolved in ethyl acetate, dried over sodium sulphate, and concentrated under reduced pressure. 5.45 g of the raw product expected are isolated, and this is made into a paste with diethyl ether. The product is filtered and dried at 70°C under vacuum. 2.781 g of the product expected are isolated. F = 1.56 ~ 1.58°C.

NMR $CDCl_3$ ppm

1.02 (t): $\underline{CH_3}$-CH_2; 1.14 (d) : 4-Me; 1.23 (d) : 8-Me; 1.27 (d) : 5'-Me; 1.30-1.34 : 6 and 12-Me; 1.78-2.02-2.04 : 2-Me-10-Me and 2'-OAc; -1.135 and 1.75 : CH_2 at 4'; ~1.49 and 1.99 : CH_2 at 7; ~1.62 and 1.83 : CH_2 at 14; ~2.70 : H_3 and H_4; 2.27 (s) : $N(Me)_2$; 3.01 (m) : H_8; 3.07 (s) : 6-OMe; 3.52 (m) : H_5; 3.70 (d) : H_3; 4.44 (d) : H_1; 4.76 (dd) : H_2; 4.81 (dd) : H_{13}; 6.28 (s, l) : H_{11}; 7.01 (dl) : H_3.

STAGE D: 2,3-didehydro-11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]-butyl]imino]]-erythromycin.

507 mg of the product obtained in Stage C, 6 ml of THF, 22.4 µl of DBU and 243 mg of CDI are stirred together. A solution is obtained, which is added to a mixture of 345 mg of aminobutylimidazolpyridine and 4 ml of methylene chloride. One drop of DBU is added and the reaction mixture is stirred for 8.5 days at 0°C. Ethyl acetate is added to the reaction mixture and the temperature is allowed to increase to ambient temperature. The mixture is washed with water, then with ammoniacal water, and then again with water. The aqueous phases are extracted with ethyl acetate, the organic phases are combined, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. 694 mg of a product are isolated, which are then dissolved in 7 ml of methanol. The solution is refluxed and concentrated under reduced pressure. 639 mg of the raw product expected are isolated, which are subjected to chromatography on silica, eluting with a 90-10 mixture of ethyl acetate/triethylamine. 292 mg of crystals are isolated, which are made into a paste with diethyl ether. The product obtained is drained, washed and dried at 50°C under reduced pressure. 170 mg of product are obtained, which are dissolved in ethyl acetate, washed in ammoniacal water, dried over anhydrous sodium sulphate and concentrated. 140 mg of crystals are obtained, which are made into a paste with ethyl acetate, washed and dried under reduced pressure at 60°C. 94 mg of the expected product are obtained. F = 196 ~ 198°C.

NMR $CDCl_3$ ppm

0.98 (t): $\underline{CH_3}$-CH_2; 1.01 (d) : 10-Me; 1.15 (d) : 8-Me;

1.25 (d) : 5'-Me; 1.28 (d) : 4-Me; 1.30 and 1.48 : 6 and 12-Me; 1.89 (sl) : 2-Me; 2.27 (s) : N-$(CH_3)_2$; 2.47 (m) : $H_{3'}$; 2.64 (m) : H_8; 2.76 (m) : H_4 2.76 (s) : 6-OMe; 3.00 (q) : H_{10} ; 3.16 (dd) : $H_{2'}$; 3.52 : H_5; 3.60 : H_5; 3.27 : H_{11}; 3.52 (m), 4.04 (m) : the CH_2-N-C=; 4.41 (d) : $H_{1'}$; 4.71 (dd) : H_{13}; 6.69 (dl) : H_3; 7.27 (dm) : H_5 - 8.10 (dt) : H_4 - 8.45 (dd) : H_6 - 9.01 (dd) : H_2 (pyridine); 7.40 (d) - 7.56 (d) (the imidazole Hs).

As a variant of the preparation process of the invention, the product (IV), namely the 2'-acetate of 11-deoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-2,3,10,11-tetradehydro-erythromycin can also be prepared as follows:

STAGE A: 3-O-de(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-11-deoxy-6.O-methyl-erythromycin.

A mixture containing 5 g of 3-O-de(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-6-O-methyl-erythromycin, 85 cm^3 of ethyl acetate, 2.8 g of ethylene carbonate and 1.1 g of dry potassium carbonate is refluxed at 160°C. Stirring is continued for 80 h. The mixture is filtered and evaporated under reduced pressure to obtain 8.54 g of the product, which is subjected to chromatography over silica, eluting with a 96/4 mixture of ethyl acetate/triethylamine. 3.07 g of the product sought are obtained.

STAGE B: 2'-acetate of 3-O-de(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-11-deoxy-6-O-methyl-erythromycin.

1.0612 g of the product from Stage A, 15 cm^3 of ethyl acetate and 0.2 cm^3 of acetic anhydride are stirred overnight at ambient temperature. 20 cm^3 of water and 4 cm^3 of ammonia are added. The mixture is extracted with ethyl acetate, washed with water, dried and concentrated. 0.9426 g of the product sought are obtained.

STAGE C: 2'-acetate-3-(methanesulphonate) of 11-deoxy-3-O-de(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-6-O-methyl-erythromycin.

At 10°C, 194 µl of mesyl chloride are added to a solution containing 600 mg of the product from Stage B, 3 cm^3 of

methylene chloride, and 404 µl of pyridine. The temperature is allowed to increase to ambient and the mixture is stirred for 8 h. The mixture is poured over ice, extracted with methylene chloride, washed with water, dried, filtered and concentrated. After chromatography and crystallisation in ether, 0.675 g of the product sought are obtained.

STAGE D: 2'-acetate of 11-deoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-2,3,10,11-tetradehydro-erythromycin.

A mixture containing 100 mg of the product prepared in the previous stage, 255 µl of DBU and 6 ml of acetone is refluxed for 24 h. The mixture is poured into water, extracted with ethyl acetate, washed with water, dried, filtered, concentrated under reduced pressure, and subjected to chromatography over silica, eluting with a 98-2 mixture of ethyl acetate/triethylamine. 51 mg of the product sought are obtained.

EXAMPLE OF PHARMACEUTICAL COMPOSITIONS

Compositions containing the following were prepared:

Product from Example 1 ..... 150 mg

Excipients, sufficient to give ..... 1 g

Details of the excipients: starch, talc, magnesium stearate.

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

Method of dilutions in a liquid medium

A series of tubes was prepared into which the same quantity of sterile nutrient medium was introduced. Increasing quantities of the product to be studied were added to each tube, and each tube was then inoculated with a bacterial strain. After incubation for 24 h in a stove at 37°C, the inhibition of growth was assessed by transmitted illumination, which makes it possible to determine the minimum inhibiting concentrations (M.I.C.) expressed in micrograms/cm^3.

The following results were obtained:

GRAM-positive bacterial strains	
Products	Ex. 1
Staphylococcus aureus 011UC4	0.08
Staphylococcus epidermidis 012GO111	0.15
Streptococcus pyogenes group A 02A1UC1	≤0.02
Streptococcus agalactiae group B 02B1HT1	≤0.02
Streptococcus faecalis group D 02D2UC1	≤0.02
Streptococcus faecium group D 02D3HT1	≤0.02
Streptococcus spp group G 02GOGR5	≤0.02
Streptococcus mitis 02 mitCB1	≤0.02
Streptococcus mitis 02 mitGR161	≤0.02
Streptococcus agalactiae group B 02B1SJ1	0.08
Streptococcus pneumoniae 030ROli	≤0.02

In addition, the product of Example 1 showed an interesting activity against the following gram-negative bacterial strains: Haemophilus influenzae 351HT3, 351CB12, 351CA1 and 351GR6.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

The following results were obtained:

GRAM-positive bacterial strains	
Products	Ex. 1
Staphylococcus aureus 011UC4	0.08
Staphylococcus epidermidis 012GO111	0.15
Streptococcus pyogenes group A 02A1UC1	≤0.02
Streptococcus agalactiae group B 02B1HT1	≤0.02
Streptococcus faecalis group D 02D2UC1	≤0.02
Streptococcus faecium group D 02D3HT1	≤0.02
Streptococcus spp group G 02GOGR5	≤0.02
Streptococcus mitis 02 mitCB1	≤0.02
Streptococcus mitis 02 mitGR161	≤0.02
Streptococcus agalactiae group B 02B1SJ1	0.08
Streptococcus pneumoniae 030ROli	≤0.02

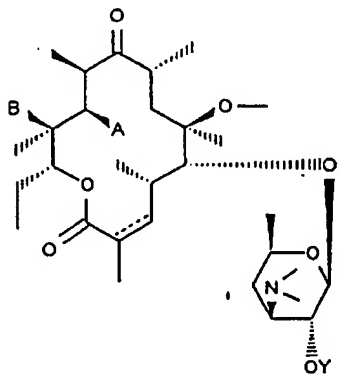
In addition, the product of Example 1 showed an interesting activity against the following gram-negative bacterial strains: Haemophilus influenzae 351HT3, 351CB12, 351CA1 and 351GR6.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

AUSTRALIAN PATENT OFFICE

The claims defining the invention are as follows:-

1) Compounds with formula (I):



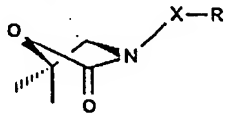
(I)

in which:

- either A and B represent an OH radical,

or B represents an OH radical and A forms a double bond with the carbon atom on which it is located and the carbon atom at 10,

- or A and B together form a carbonate radical,
- or A and B together with the carbon atoms on which they are located form a cycle:



in which X represents a CH_2, NH or SO_2 group, R represents a $(CH_2)_n$ Ar, $N=CH(CH_2)_nAr$ $N = (CH_2)_n$ Ar radical, in which n is an integer between 1 and 6 and Ar represents an aryl or heteroaryl radical, possibly substituted, the broken lines represent a possible double bond at 2(3), and Y represents a hydrogen atom or the residue of a carboxylic organic acid containing up to 18 carbon atoms, and their addition salts with acids.

2) Compounds with formula (I) as defined in Claim 1, corresponding to formula (I), in which X represents

AUSTRALIAN PATENT OFFICE

a CH_2 or NH group, R represents a $(CH_2)_n$ Ar, N-$(CH_2)_n$ Ar or N = CH$(CH_2)_n$ Ar radical, in which n is an integer between 1 and 6 and Ar represents a possibly substituted aryl or heteroaryl radical, the broken lines represent a possible double bond at 2(3), and Y represents a hydrogen atom or the residue of a carboxylic organic acid containing up to 18 carbon atoms, and their addition salts with acids.

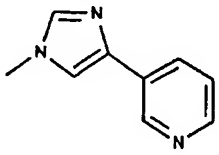
3) The compounds with formula (I) as defined in Claims 1 or 2, in which the broken lines represent a double bond at 2(3).

4) The compounds with formula (I) as defined in Claims 1, 2 or 3, in which Y represents a hydrogen atom.

5) The compounds with formula (I) as defined in any of Claims 2 to 4, in which R represents a $(CH_2)_n$ Ar group, where n and Ar have the same meaning as in Claim 1.

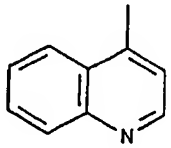
6) The compounds with formula (I) as defined in any of Claims 2 to 5, in which R represents a $(CH_2)_3$ Ar, $(CH_2)_4$ Ar or $(CH_2)_5$ Ar radical.

7) The compounds with formula (I) as defined in any of Claims 2 to 6, in which Ar represents a possibly substituted:



radical,

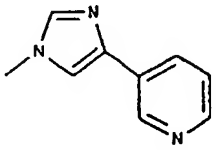
or a possibly substituted:



radical.

AUSTRALIAN PATENT OFFICE

8) The compounds with formula (I) as defined in Claim 7, in which Ar represents a:



radical.

9) The compounds with formula (I) as defined in Claim 1, whose name is given below:

2,3-didehydro-11,12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]-imino]]-erythromycin.

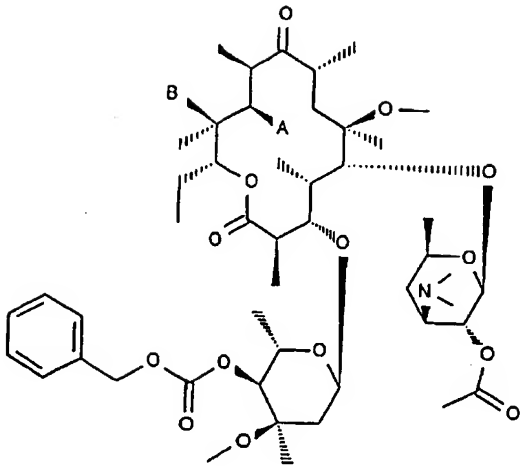
10) As medicaments, the compounds with formula (I) defined in any of Claims 1 to 8, and their addition salts with pharmaceutically acceptable acids.

11) As a medicament, the compound defined in Claim 9, and its addition salts with pharmaceutically acceptable acids.

12) Pharmaceutical compositions containing as the active ingredient at least one medicament as defined in Claims 10 to 11.

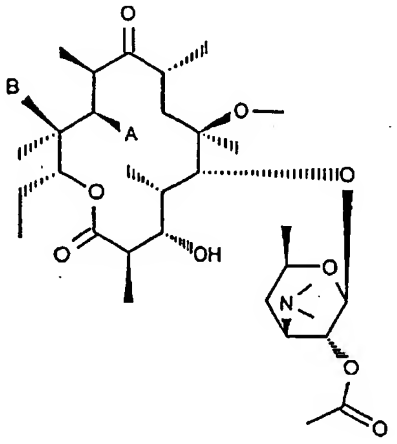
13) Process for the preparation of compounds with formula (I), characterised in that a compound with formula (II):

AUSTRALIAN PATENT OFFICE



(II)

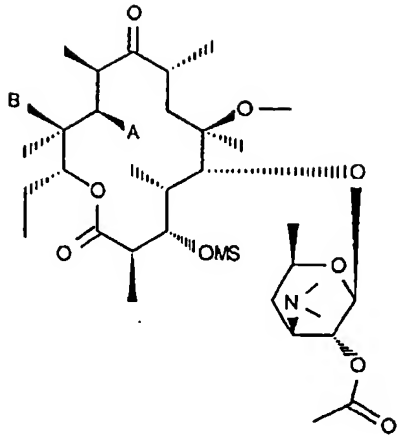
in which A and B have the same meanings as before is subjected to the action of an agent which splits the glycoside bond to free the hydroxyl at 3 and obtain a compound with formula (III):



(III)

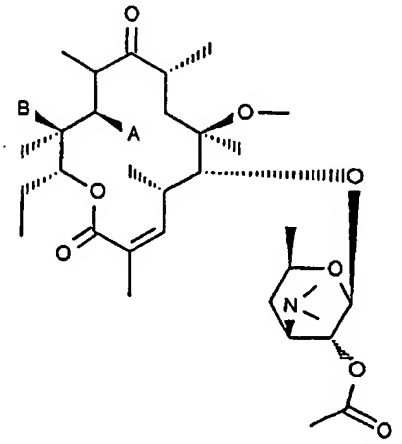
and blocks the hydroxyl at 3 in the form of a mesylate to obtain the compound with formula (IV):

AUSTRALIAN PATENT OFFICE



(IV)

which is subjected to the action of a base to obtain the compound with formula (V):

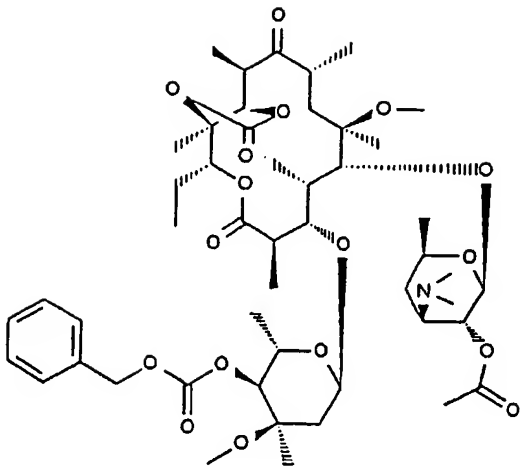


(V)

which, if desired, is subjected to the action of an agent which splits the hydroxyl at 2' to obtain the corresponding compound with formula (I).

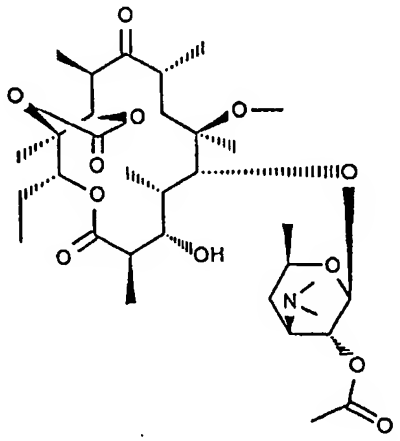
14) Process for preparing compounds with formula (I), characterised in that a compound with formula (II_A):

AUSTRALIAN PATENT OFFICE



(II_A)

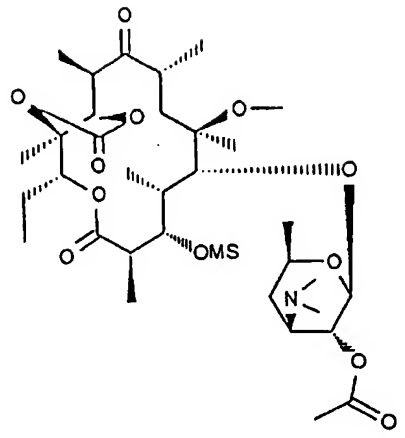
is subjected to the action of an agent which splits the glycoside bond to free the hydroxyl at 3 and obtain a compound with formula (III_A):



(III_A)

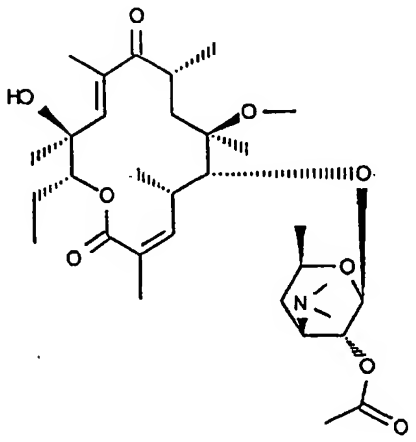
and blocks the hydroxyl at 3 in the form of a mesylate to obtain the compound with formula (IV_A):

AUSTRALIAN PATENT OFFICE



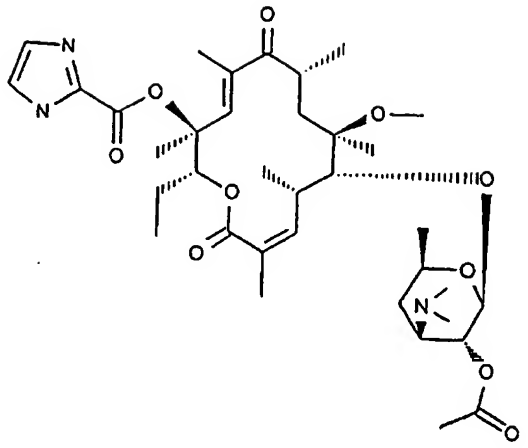
(IV_A)

which is subjected to the action of a base to obtain the compound with formula (V_A):



(V_A)

which is subjected to the action of carbonydiimidazole to obtain the compound with formula (VI):

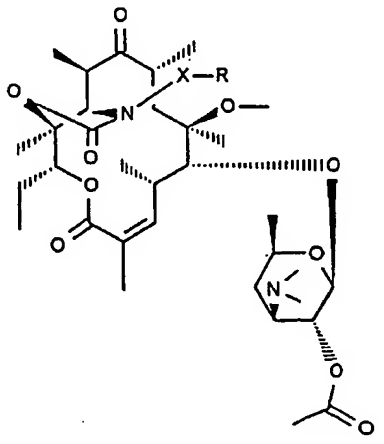


(VI)

which is subjected to the action of the compound with formula (VII):

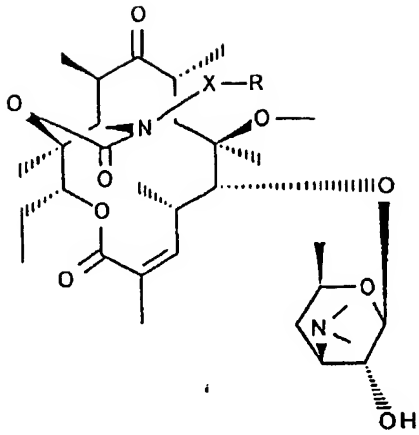
$$RXNH_2 \qquad (VII)$$

in which R and X mean the same as before, to obtain the compound with formula (I_A):



(I_A)

and, if desired, to free the hydroxyl at 2' to obtain the compound with formula (I_H):



(I_B)

which, if desired, is subjected to the action of an agent that esterifies the hydroxyl at 2′, and/or to the action of an agent that reduces the double bond at 2(3), and/or to the action of an acid to form the salt thereof.

15) As new chemical products, the compounds with formulae (IV), (V), and (VI) defined in Claims 13 or 14.

16) As new chemical products defined in Claim 15, the following products:

- cyclic 11,12-carbonate 2′-acetate 3-(methanesulphonate) of 3-O-de(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)-6-O-methyl-erythromycin,

- 2′-acetate of 11,deoxy-3-de[(2,6-didcoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl)oxy]-6-O-methyl-2,3,10,11-tetradehydro-erythromycin.

AUSTRALIAN PATENT OFFICE

17. Compounds as defined in any one of claims 1 to 9 or medicaments including the same substantially as hereinbefore described with reference to any one of the examples.

18. Process as defined in claim 13 or claim 14 substantially as hereinbefore described with reference to any one of the examples.

DATED this 23rd day of August, 2000.

HOECHST MARION ROUSSEL
By their Patent Attorneys:
CALLINAN LAWRIE